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(54) Title: NITROOXYDERIVATIVES OF ANTIHYPERTENSIVE DRUGS

(57) Abstract: The present invention relates to β-adrenergic blockers nitrooxyderivatives of general formula (I): A-(Y-ONO_2), and enantiomers and diastereoisomers and pharmaceutically acceptable salts thereof, pharmaceutical compositions containing them and their use for the treatment of hypertension, cardiovascular diseases, glaucoma, migraine headache and vascular diseases.

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Title

Nitrooxyderivatives of Antihypertensive drugs

The present invention relates to β-adrenergic blockers derivatives. More particularly, the present invention relates to β-adrenergic blockers nitrooxyderivatives, pharmaceutical compositions containing them and their use for the treatment of hypertension, cardiovascular diseases, glaucoma, migraine headache, vascular diseases and elevated intraocular pressure.

β-adrenergic blockers (β-blockers) are widely used in the treatment of hypertension and cardiovascular diseases including angina pectoris, arrhythmias, acute myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure.

They work to block the effects of catecholamines at receptor sites in the heart, but they differ somewhat in their ability to block receptors in the blood vessels and lungs . Selective β-blockers have their major actions on the heart, some others are weak stimulators of the β-receptor while still blocking the major actions of catecholamines, some block both the β_1 and β_2 receptors in the heart and those in the blood vessels and have no stimulatory activity and some block other cathecolamine receptors that can lead to further vascular effects on blood vessels.

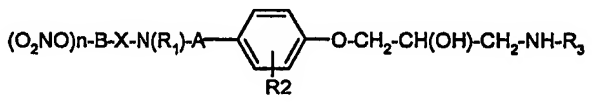
Several side effects are associated with this class of drugs such as muscle fatigue, sleep disturbances, decreased heart rate, hypotension, cold extremities, bronchospasm in asthmatic patients, hypoglycaemia, increased lipids in plasma.

Moreover, abrupt withdrawal after long-term treatment with beta-blockers has to be avoided, because an increased sensitivity to β-adrenergic system develops.

U.S. Pat. No. 6,242,432 discloses derivatives of formula $A-(X_1-NO_2)_{to}$ having an antithrombotic activity, wherein A is the residue of a β-adrenergic blocker, X_1 is a bivalent connecting bridge and t_o is 1 or 2. The invention is limited to particular meanings of the bivalent connecting bridge X_1.

U.S. Pat . No 5,502,237 and U.S. Pat. No 5,639,904 disclose derivatives of formula R_1-Ar-O-CH_2-CH(OH)-CH_2-NH-$CH(CH_3)_2$ used for the treatment of cardiovascular affections, wherein R_1 is a chain having at least one nitrooxy group as substituent.

U.S. Pat. No. 4,801,596 discloses aminopropanol derivatives of formula



that can be used for prophylaxis and/or treatment of heart and circulatory diseases, wherein R_3 is an alkyl or a nitroxyalkyl radical containing 3 to 8 carbon atoms.

It was an object of the present invention to provide new β-adrenergic blockers nitroxyderivatives having a significantly improved overall pharmacological profile as compared to native β-blockers that are able not only to eliminate or at least reduce the side effects associated with their parent compounds, but also having an improved pharmacological activity and tolerability.

It has been so surprisingly found that the β-adrenergic blockers nitrooxyderivatives of the present invention have a better pharmacological activity and organ protection properties, enhanced effects as anti-inflammatory, and on renal functions. In addition, they are effective in other pathologies including atherosclerosis, diabetes, peripheral vascular diseases (PVD) and elevated intraocular pressure.

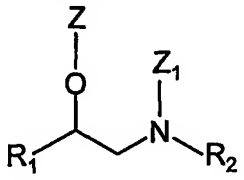
In particular, it has been recognized that the β-adrenergic blockers nitrooxyderivatives of the present invention, differently from the above mentioned compounds of the prior art, exhibit an improved activity on the cardiovascular system and enhanced tolerability and can be employed for treating or preventing hypertension, cardiovascular diseases, glaucoma, migraine headache, vascular diseases and elevated intraocular pressure..

Object of the present invention are β-adrenergic blockers nitrooxyderivatives of general formula (I):

$$A\text{-}(Y\text{-}ONO_2)_s$$

and enantiomers and diastereoisomers and pharmaceutically acceptable salts thereof, wherein s is an integer equal to 1 or 2, preferably s is 2;

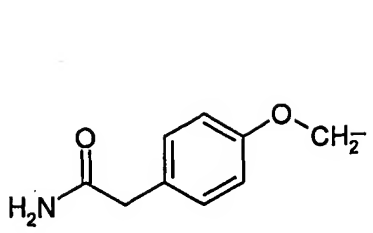
A is selected from the following β-adrenergic blocker residues of formula (II):



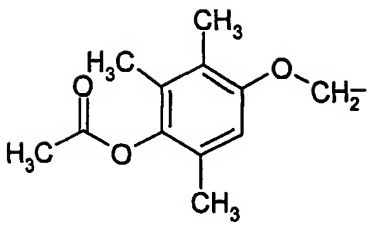
(II)

wherein

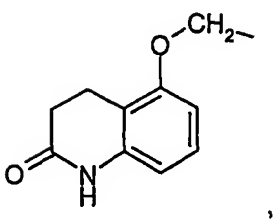
R_1 is selected from the group consisting of:



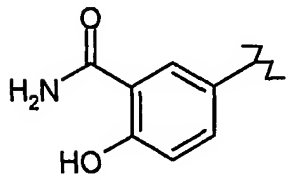
(IIo)



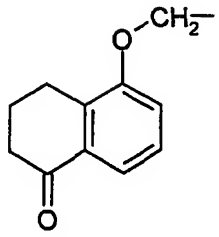
(IIp)



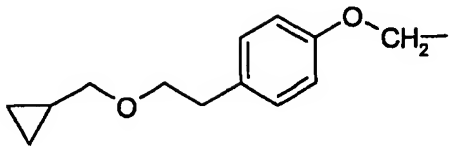
(IIq)



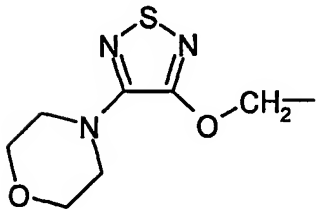
(IIr)



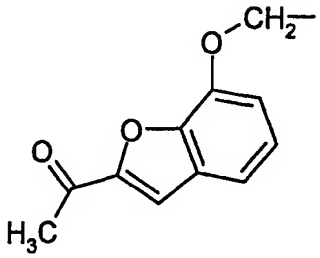
(IIs)



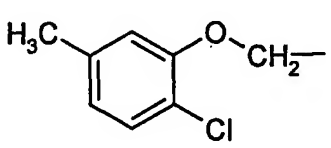
(IIt)



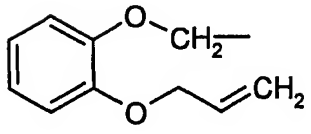
(IIu)



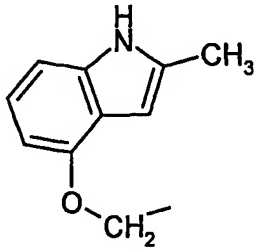
(IIv)



(IIw)

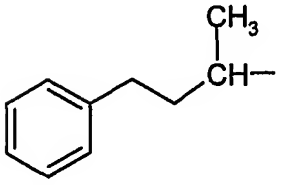


(IIy)



(IIz);

R_2 is selected from the group consisting of: $-CH(CH_3)_2$, $-C(CH_3)_3$ or



;

(IIIc)

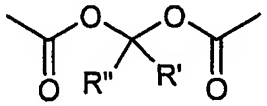
when the radical R_1 has chosen from the formulae (IIo), (IIp), (IIt), (IIu), (IIv), (IIy) or (IIz), R_2 is $-CH(CH_3)_2$;

when the radical R_1 has chosen from the formulae (IIq), (IIs) or (IIw), R_2 is $-C(CH_3)_3$;

when the radical R_1 is (IIr), R_2 is (IIIc);

Z is H or is a group capable of binding Y selected from the group consisting of:

–C(O)-, –C(O)O- or



wherein R' and R" are the same or different, and are H or straight or branched C_1-C_4 alkyl;

Z_1 is H or a –C(O)- group capable of binding Y;

with the proviso that when s of formula (I) is 1 Z or Z_1 is H;

when s is 2, Z and Z_1 are preferably –C(O)-;

Y is a bivalent radical having the following meaning:

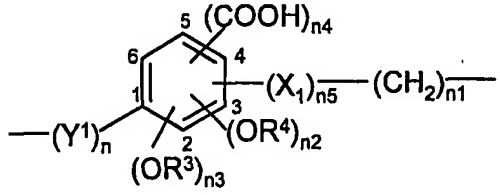
a)

- straight or branched C_1-C_{20} alkylene, preferably C_1-C_{10}, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $-ONO_2$ or T, wherein T is $-OC(O)(C_1$-C_{10}alkyl)-ONO_2, $-O(C_1$-C_{10}alkyl)-ONO_2;

b)

- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T_1, wherein T_1 is straight or branched alkyl with from 1 to 10 carbon atoms, T_1 is preferably CH_3;

c)



(IV)

wherein:

n is an integer from 0 to 20, preferably n is an integer from 0 to 10, more preferably n is 0, and n1 is an integer from 1 to 20, preferably from 1 to 10;

n2, n3, n4 and n5 are integers equal or different from each others, equal to 0 or 1;

R^3 and R^4 are independently selected from H or CH_3;

Y^1 is $–CH_2$- or $–(CH_2)_{na}$-CH=CH- wherein na is an integer from 0 to 20, preferably na is equal to 0;

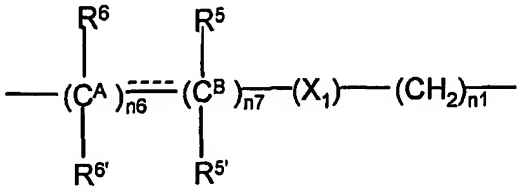
X_1 is –WC(O)- or –C(O)W-, wherein W is oxygen, sulfur or NH, preferably W is oxygen;

with the proviso that:

- when s of formula (I) is 1, Z is –(CO)- and in formula (IV) of the bivalent radical Y n2, n3, n4, n5 are equal to 0 then n is 0 and n1 is 1;

- when s of formula (I) is 1, Z is –(CO)- and in formula (IV) of the bivalent radical Y n2, n3, n5 are equal to 0, n4 is 1 then n and n1 are different to 1;

d)



(V)

wherein:

n1 is an integer from 1 to 20, preferably from 1 to 10;

X_1 is –WC(O)- or –C(O)W-, wherein W is oxygen, sulfur or NH, preferably W is sulfur;

n6 is an integer from 1 to 20,

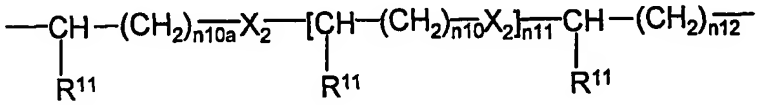
n7 is an integer from 0 to 20,

R^5 and $R^{5'}$ R^6 and $R^{6'}$ are independently selected from the group consisting of: H, CH_3, OH, NH_2, $NHCOCH_3$, COOH, CH_2SH and $C(CH_3)_2SH$; when the bond between the C^A and C^B carbons is a double bond R^5 and R^6 or $R^{6'}$ and $R^{5'}$ are absent;

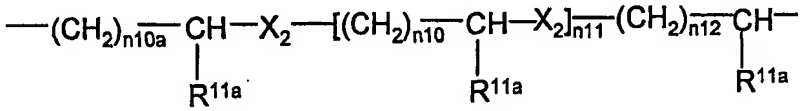
with the proviso that when Y is selected from the bivalent radicals mentioned under c)-d), the $–ONO_2$ group is linked to a $–(CH_2)_{n1}$- group;

with the proviso that when s of formula (I) is 1 and Z is –(CO)- then the bivalent radical Y has not the meanings under a), b) and d);

e)



(VI)



(VII)

wherein X_2 is O or S,

n10a, n10 and n12 are integer independently selected from 0 to 20,

n10a is preferably selected from 0 to 10,

n10 and n12 are preferably selected from 1 to 10, and

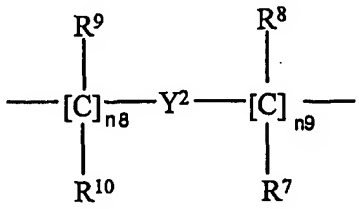
n11 is an integer from 0 to 6, preferably from 0 to 4,

R^{11} is H, CH_3 or nitrooxy group, preferably R^{11} is H,

R^{11a} is CH_3 or nitrooxy group;

with the proviso that when in formula (I) s is 1, in formula (II) Z is –(CO)-, in formula (VI) of the bivalent radical Y n10a, n10, n12 are equal to 1 then X can not be an oxygen atom;

f)



(VIII)

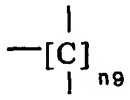
wherein

n8 is an integer from 0 to 10;

n9 is an integer from 1 to 10;

R^9, R^{10}, R^8, R^7 are same or different, and are H or straight or branched C_1-C_4 alkyl, preferably R^9, R^{10}, R^8, R^7 are H;

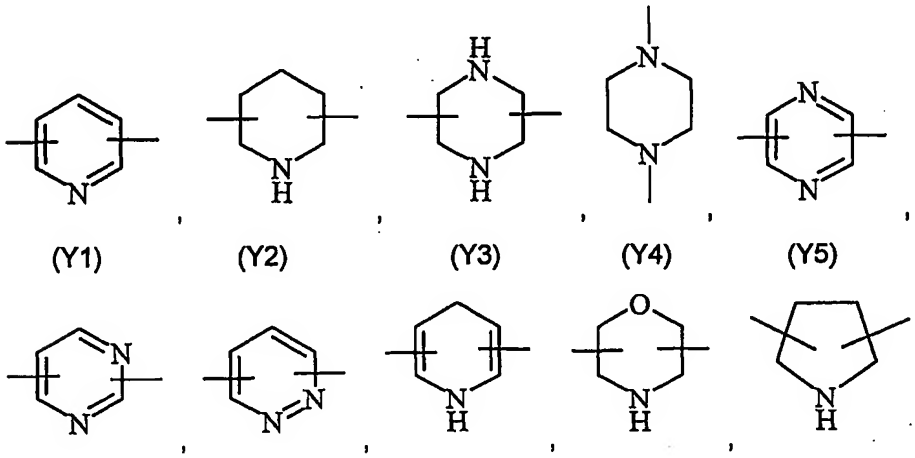
wherein the $–ONO_2$ group is linked to



wherein n9 is as defined above;

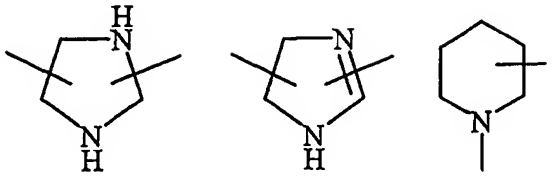
Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatom/s selected from nitrogen, oxygen, sulfur,

and is selected from the group consisting of



(Y1) (Y2) (Y3) (Y4) (Y5)

(Y6) (Y7) (Y8) (Y9) (Y10)



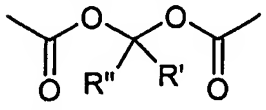
(Y11) (Y12) (Y13)

One embodiment of the present invention comprises compounds of formula (I) wherein s is 2,

A is a β-adrenergic blocker residue of formula (II) as above defined:

Z is a group capable of binding Y selected from the group consisting of:

–C(O)-, –C(O)O- or



wherein R' and R" are the same or different, and are H or straight or branched C_1-C_4 alkyl;

Z_1 is –C(O)-;

preferably Z and Z_1 are –C(O)-;

Y is a bivalent radical having the following meaning:

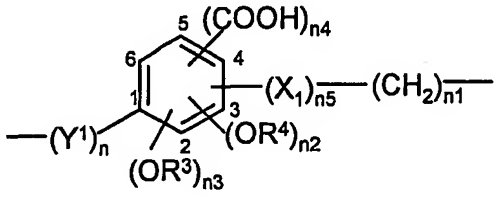
a)

- straight or branched C_1-C_{20} alkylene, preferably C_1-C_{10}, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $–ONO_2$ or T, wherein T is $–OC(O)(C_1$-C_{10}alkyl)-ONO_2, $–O(C_1$-C_{10}alkyl)-ONO_2;

b)

- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T_1, wherein T_1 is straight or branched alkyl with from 1 to 10 carbon atoms, T_1 is preferably CH_3;

c)



(IV)

wherein:

n is an integer from 0 to 20, preferably n is an integer from 0 to 10, more preferably n is 0, and n1 is an integer from 1 to 20, preferably from 1 to 10;

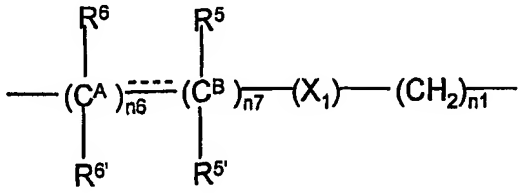
n2, n3, n4 and n5 are integers equal or different from each others, equal to 0 or 1;

R^3 and R^4 are independently selected from H or CH_3;

Y^1 is $-CH_2-$ or $-(CH_2)_{na}-CH=CH-$ wherein na is an integer from 0 to 20, preferably na is equal to 0;

X_1 is –WC(O)- or –C(O)W-, wherein W is oxygen, sulfur or NH, preferably W is oxygen;

d)



(V)

wherein:

n1 is an integer from 1 to 20, preferably from 1 to 10;

X_1 is –WC(O)- or –C(O)W-, wherein W is oxygen, sulfur or NH, preferably W is sulphur;

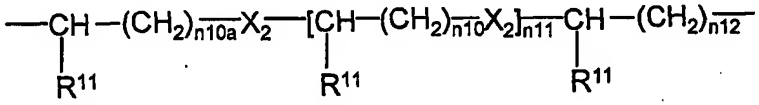
n6 is an integer from 1 to 20, preferably n6 is 1,

n7 is an integer from 0 to 20, preferably n7 is 1,

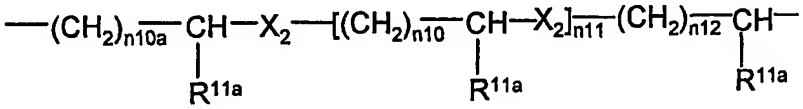
R^5 and $R^{5'}$ R^6 and $R^{6'}$ are independently selected from the group consisting of: H, CH_3, OH, NH_2, $NHCOCH_3$, COOH, CH_2SH and $C(CH_3)_2SH$; when the bond between the C^A and C^B carbons is a double bond R^5 and R^6 or $R^{6'}$ and $R^{5'}$ are absent;

with the proviso that when Y is selected from the bivalent radicals mentioned under c)-d), the $-ONO_2$ group is linked to a $-(CH_2)_{n1}-$ group;

e)



(VI)



(VII)

wherein X_2 is O or S,

n10a, n10 and n12 are integer independently selected from 0 to 20,

n10a is preferably selected from 0 to 10,

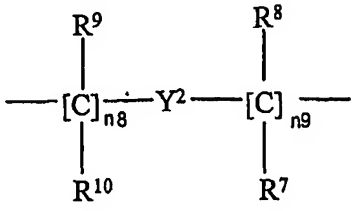
n10 and n12 are preferably selected from 1 to 10, and

n11 is an integer from 0 to 6, preferably from 0 to 4,

R^{11} is H, CH_3 or nitrooxy group, preferably R^{11} is H,

R^{11a} is CH_3 or nitrooxy group;

f)



(VIII)

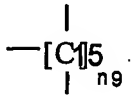
wherein

n8 is an integer from 0 to 10;

n9 is an integer from 1 to 10;

R^9, R^{10}, R^8, R^7 are same or different, and are H or straight or branched C_1-C_4 alkyl, preferably R^9, R^{10}, R^8, R^7 are H;

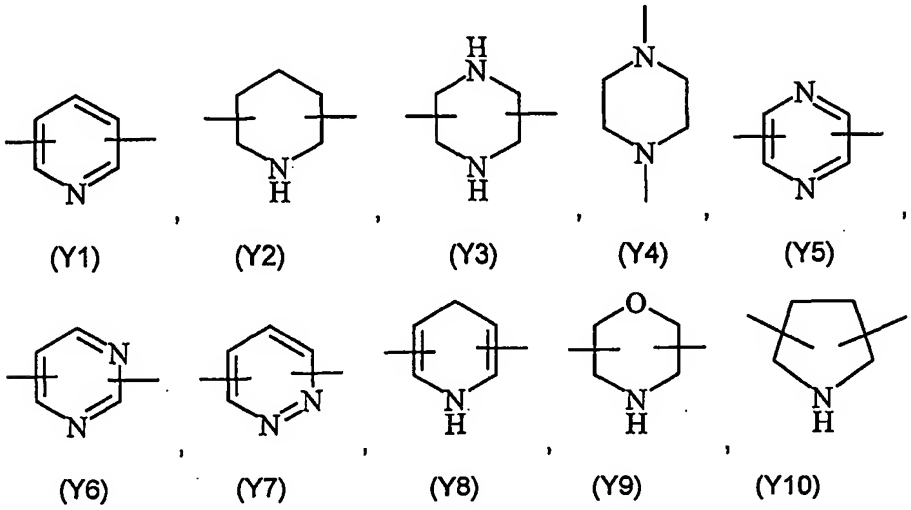
wherein the $-ONO_2$ group is linked to



wherein n9 is as defined above;

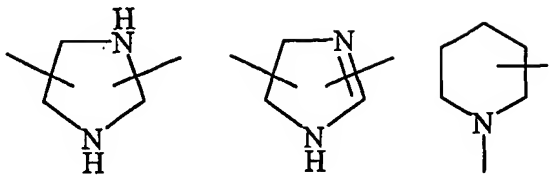
Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatom/s selected from nitrogen, oxygen, sulfur,

and is selected from the group consisting of



(Y1) (Y2) (Y3) (Y4) (Y5)

(Y6) (Y7) (Y8) (Y9) (Y10)



(Y11) (Y12) (Y13)

Another embodiment comprises compounds of formula (I) wherein

s is 1,

A is a β-adrenergic blocker residue of formula (II) as above defined:

Z is H,

Z_1 is –C(O)-;

Y is a bivalent radical having the following meaning:

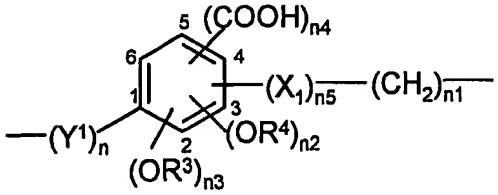
a)

- straight or branched C_1-C_{20} alkylene, preferably C_1-C_{10}, more preferably C_3-C_6 being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $–ONO_2$ or T, wherein T is $–OC(O)(C_1$-C_{10}alkyl)-ONO_2, $–O(C_1$-C_{10}alkyl)-ONO_2;

b)

- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T_1, wherein T_1 is straight or branched alkyl with from 1 to 10 carbon atoms, T_1 is preferably CH_3;

c)



(IV)

wherein:

n is an integer from 0 to 20, preferably n is an integer from 0 to 10, more preferably n is 0, and n1 is an integer from 1 to 20, preferably from 1 to 10;

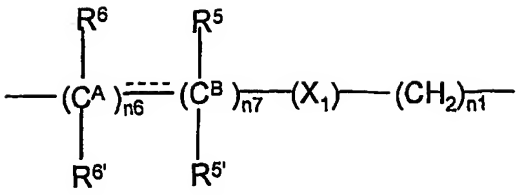
n2, n3, n4 and n5 are integers equal or different from each others, equal to 0 or 1;

R^3 and R^4 are independently selected from H or CH_3;

Y^1 is $–CH_2$- or $–(CH_2)_{na}$-CH=CH- wherein na is an integer from 0 to 20, preferably na is equal to 0;

X_1 is –WC(O)- or –C(O)W-, wherein W is oxygen, sulfur or NH, preferably W is oxygen;

d)



(V)

wherein:

n1 is an integer from 1 to 20, preferably from 1 to 10;

X_1 is –WC(O)- or –C(O)W-, wherein W is oxygen, sulfur or NH, preferably W is sulfur;

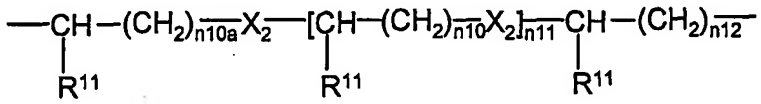
n6 is an integer from 1 to 20,

n7 is an integer from 0 to 20,

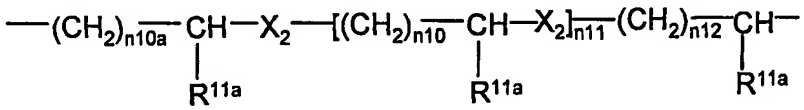
R^5 and $R^{5'}$ R^6 and $R^{6'}$ are independently selected from the group consisting of: H, CH_3, OH, NH_2, $NHCOCH_3$, COOH, CH_2SH and $C(CH_3)_2SH$; when the bond between the C^A and C^B carbons is a double bond R^5 and R^6 or $R^{6'}$ and $R^{5'}$ are absent;

with the proviso that when Y is selected from the bivalent radicals mentioned under c)-d), the $-ONO_2$ group is linked to a $-(CH_2)_{n1}$- group;

e)



(VI)



(VII)

wherein X_2 is O or S,

n10a, n10 and n12 are integer independently selected from 0 to 20,

n10a is preferably selected from 0 to 10,

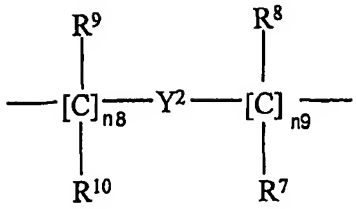
n10 and n12 are preferably selected from 1 to 10, and

n11 is an integer from 0 to 6, preferably from 0 to 4,

R^{11} is H, CH_3 or nitrooxy group, preferably R^{11} is H,

R^{11a} is CH_3 or nitrooxy group;

f)



(VIII)

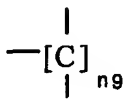
wherein

n8 is an integer from 0 to 10;

n9 is an integer from 1 to 10;

R^9, R^{10}, R^8, R^7 are same or different, and are H or straight or branched C_1-C_4 alkyl, preferably R^9, R^{10}, R^8, R^7 are H;

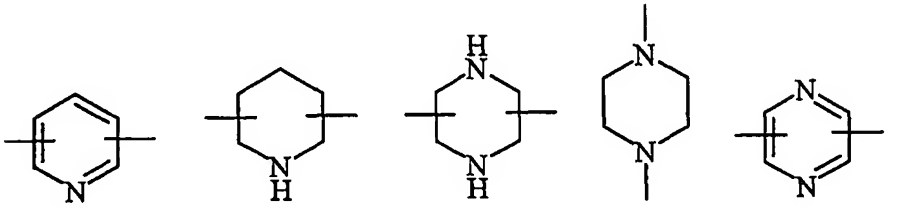
wherein the $-ONO_2$ group is linked to



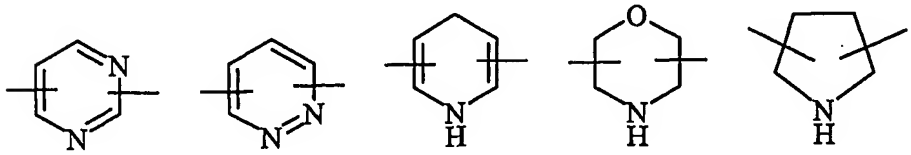
wherein n9 is as defined above;

Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatom/s selected from nitrogen, oxygen, sulfur,

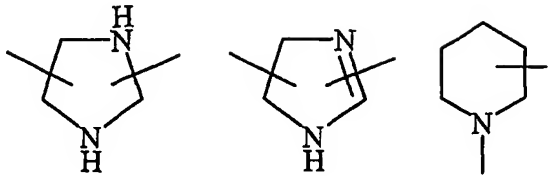
and is selected from the group consisting of



(Y1) (Y2) (Y3) (Y4) (Y5)



(Y6) (Y7) (Y8) (Y9) (Y10)



(Y11) (Y12) (Y13)

Another embodiment comprises compounds of formula (I) wherein

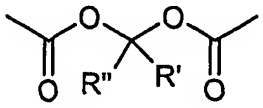
s is 1,

A is a β-adrenergic blocker residue of formula (II) as above defined:

Z_1 is H,

Z is a group capable of binding Y selected from the group consisting of:

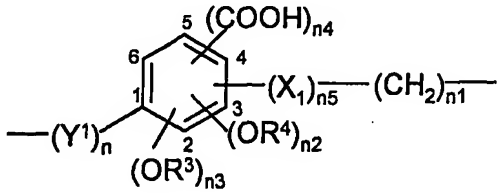
–C(O)-, –C(O)O- or



wherein R' and R" are the same or different, and are H or straight or branched C_1-C_4 alkyl; preferably Z is –C(O)-;

Y is a bivalent radical having the following meaning:

c)



(IV)

wherein:

n is an integer from 0 to 20, preferably n is an integer from 0 to 10, more preferably n is 0, and n1 is an integer from 1 to 20, preferably from 1 to 10;

n2, n3, n4 and n5 are integers equal or different from each others, equal to 0 or 1;

R^3 and R^4 are independently selected from H or CH_3;

Y^1 is $–CH_2–$ or $–(CH_2)_{na}–CH=CH–$ wherein na is an integer from 0 to 20, preferably na is equal to 0;

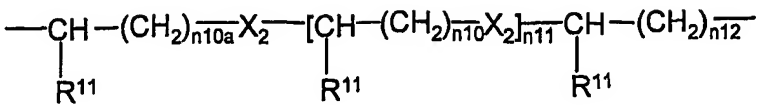
X_1 is –WC(O)- or –C(O)W-, wherein W is oxygen, sulfur or NH, preferably W is oxygen;

with the proviso that when Z is –C(O)-:

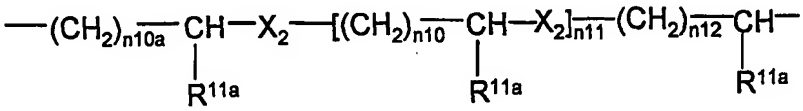
- in the bivalent radical Y of formula (IV) n2, n3, n4, n5 are equal to 0 then n is 0 and n1 is 1;

- in the bivalent radical Y of formula (IV) n2, n3, n5 are equal to 0, n4 is 1 then n and n1 are different to 1;

e)



(VI)



(VII)

wherein X_2 is O or S,

n10a, n10 and n12 are integer independently selected from 0 to 20,

n10a is preferably selected from 0 to 10,

n10 and n12 are preferably selected from 1 to 10, and

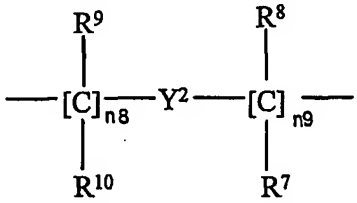
n11 is an integer from 0 to 6, preferably from 0 to 4,

R^{11} is H, CH_3 or nitrooxy group, preferably R^{11} is H,

R^{11a} is CH_3 or nitrooxy group;

with the proviso that when Z is –C(O)- and in formula (VI) of the bivalent radical Y n10a, n10, n12 are equal to 1 then X can not be an oxygen atom;

f)



(VIII)

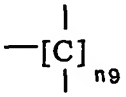
wherein

n8 is an integer from 0 to 10;

n9 is an integer from 1 to 10;

R^9, R^{10}, R^8, R^7 are same or different, and are H or straight or branched C_1-C_4 alkyl, preferably R^9, R^{10}, R^8, R^7 are H;

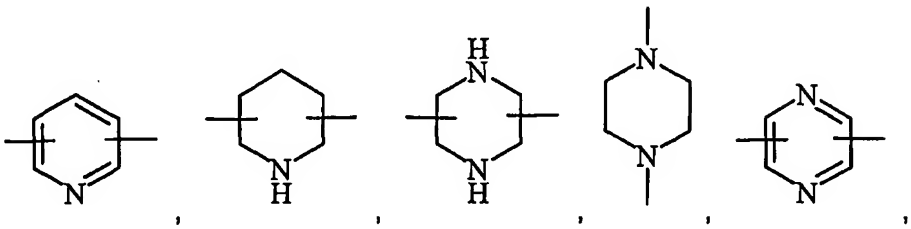
wherein the $-ONO_2$ group is linked to



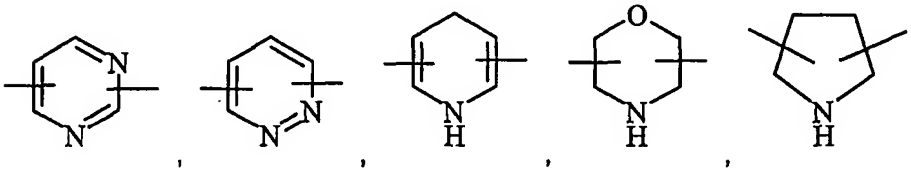
wherein n9 is as defined above;

Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatom/s selected from nitrogen, oxygen, sulfur,

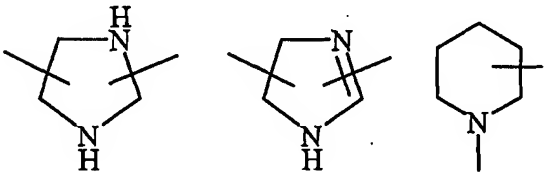
and is selected from the group consisting of



(Y1) (Y2) (Y3) (Y4) (Y5)



(Y6) (Y7) (Y8) (Y9) (Y10)



(Y11) (Y12) (Y13)

Preferred compounds are those of formula (I) wherein

s is 1

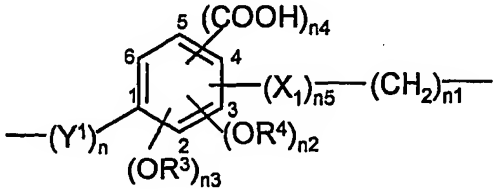
A is a β-adrenergic blocker residue of formula (II) as above defined,

Z is H and Z_1 is –C(O)-,

and the bivalent radical Y have the following meaning:

a) straight C_1-C_{10} alkylene, preferably C_3-C_6 alkylene;

c)



(IV)

wherein the $-ONO_2$ group is bound to $(CH_2)_{n1}$;

n, n2, n3, n4, n5 are equal to 0,

n1 is 1 and the $-(CH_2)_{n1}-$ group is bound to the phenyl ring through the $[C]_2$ or the $[C]_3$ or the $[C]_4$; or

n, n2, n5 are 1,

n3 and n4 are equal to 0, and

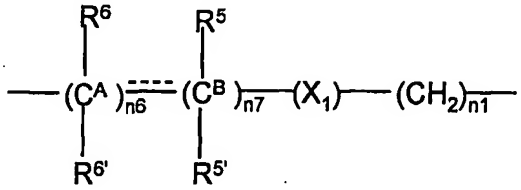
n1 is an integer from 1 to 10,

Y^1 is $-(CH_2)_{na}-CH=CH-$ wherein na is 0,

X_1 is $-WC(O)-$ wherein W is oxygen and the WC(O) group is bound to the phenyl ring through the $[C]_4$,

R^4 is CH_3 and the (OR^4) group is bound to the phenyl ring through the $[C]_3$;

d)



(V)

wherein

the $-ONO_2$ is bound to the $-(CH_2)_{n1}-$ group;

n1 is an integer from 1 to 10, n6 and n7 are 1, X_1 is $-WC(O)-$ wherein W is sulfur,

R^5, $R^{5'}$ and $R^{6'}$ are H,

R^6 is $NHCOCH_3$.

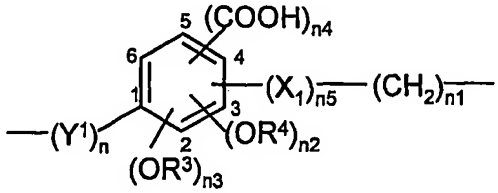
Another group of preferred compounds are those of formula (I) wherein s is 1,

A is a β-adrenergic blocker residue of formula (II) as above defined,

Z_1 is H and Z is $-C(O)-$, and

the bivalent radical Y have the following meaning:

c)



(IV)

wherein the $-ONO_2$ group is bound to $(CH_2)_{n1}$;

n, n2, n3, n4, n5 are equal to 0,

n1 is 1 and the -$(CH_2)_{n1}$- group is bound to the phenyl ring through the $[C]_2$ or the $[C]_3$ or the $[C]_4$; or

n, n2, n5 are 1,

n3 and n4 are equal to 0, and

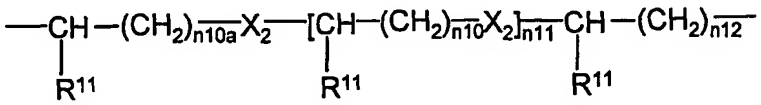
n1 is an integer from 1 to 10,

Y^1 is $-(CH_2)_{na}$-CH=CH- wherein na is 0,

X_1 is –WC(O)- wherein W is oxygen and the WC(O) group is bound to the phenyl ring through the $[C]_4$,

R^4 is CH_3 and the (OR^4) group is bound to the phenyl ring through the $[C]_3$;

d)



(VI)

wherein

X_2 is O or S, and n10a and n11 are 0, n12 is 1 and R^{11} is H and the -ONO_2 group is bound to $(CH_2)_{n12}$.

Another group of preferred compounds are those of formula (I) wherein s is 2,

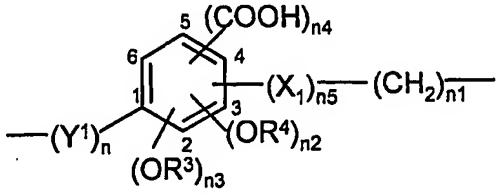
A is a β-adrenergic blocker residue of formula (II) as above defined,

Z_1 and Z are –C(O)-, and

the bivalent radical Y have the following meaning:

a) straight C_1-C_{10} alkylene, preferably C_3-C_6 alkylene;

c)



(IV)

wherein the -ONO_2 group is bound to $(CH_2)_{n1}$;

n, n2, n3, n4, n5 are equal to 0,

n1 is 1 and the -$(CH_2)_{n1}$- group is bound to the phenyl ring through the $[C]_2$ or the $[C]_3$ or the $[C]_4$;

or n, n2, n5 are 1,

n3 and n4 are equal to 0, and

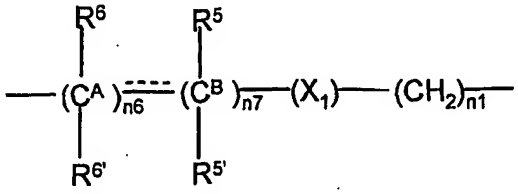
n1 is an integer from 1 to 10,

Y^1 is $-(CH_2)_{na}$-CH=CH- wherein na is 0,

X_1 is –WC(O)- wherein W is oxygen and the WC(O) group is bound to the phenyl ring through the $[C]_4$,

R^4 is CH_3 and the (OR^4) group is bound to the phenyl ring through the $[C]_3$;

d)



(V)

wherein

the -ONO_2 is bound to the -$(CH_2)_{n1}$- group;

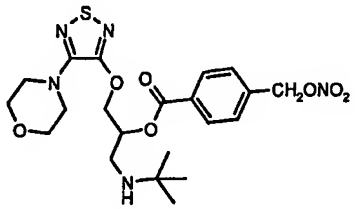
n1 is an integer from 1 to 10,

n6 and n7 are 1,

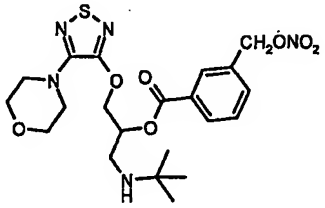
X_1 is –WC(O)- wherein W is sulfur,

R^5, $R^{5'}$ and $R^{6'}$ are H, R^6 is $NHCOCH_3$.

Preferred compounds of formula (I) according to the present invention are the following:



(1)



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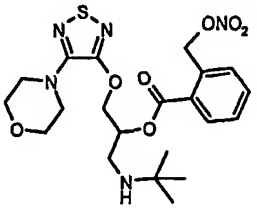

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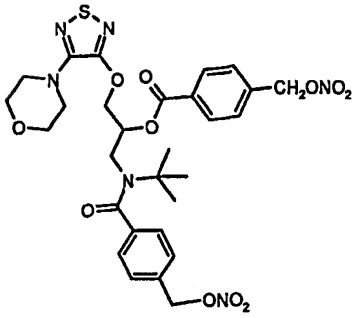

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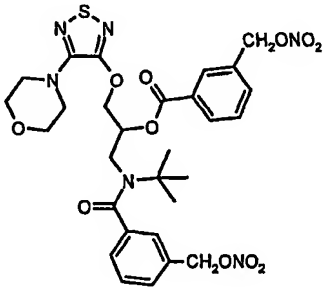

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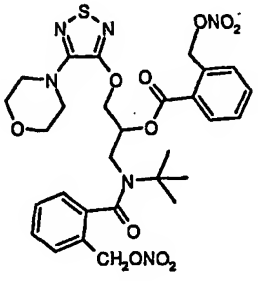

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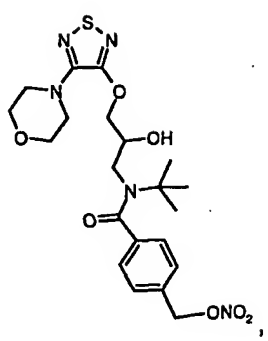
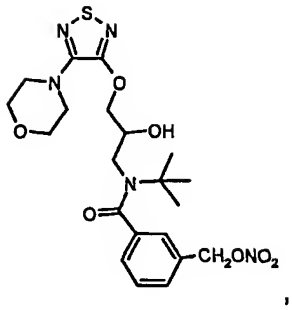


(7)



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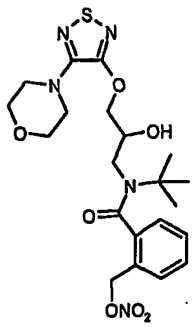


(9)

Examples of "straight or branched C_1-C_{20} alkylene" include, but are not limited to, methylene, ethylene, propylene, isopropylene, n-butylene, pentylene, n-hexylene and the like.

As stated above, the invention includes also the pharmaceutically acceptable salts of the compounds of formula (I) and stereoisomers thereof.

Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminium hydroxides, or with organic bases, such as lysine, arginine, triethylamine, dibenzylamine, piperidine and other acceptable organic amines.

The compounds according to the present invention, when they contain in the molecule one salifiable nitrogen atom, can be transformed into the corresponding salts by reaction in an organic solvent such as acetonitrile, tetrahydrofuran with the corresponding organic or inorganic acids.

Examples of pharmaceutical acceptable organic acids are: oxalic, tartaric, maleic, succinic, citric acids. Examples of pharmaceutical acceptable inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acids. Salts with nitric acid are preferred.

The compounds of the invention which have one or more asymmetric carbon atoms can exist as optically pure enantiomers, pure diastereomers, enantiomers mixtures, diastereomers mixtures, enantiomer racemic mixtures, racemates or racemate mixtures. Within the object of the invention are also all the possible isomers, stereoisomers and their mixtures of the compounds of formula (I).

The compounds and compositions of the present invention can be administered by any available and effective delivery system including but not limited to, orally, bucally, parenterally, by inhalation spray, by topicall application, by injection, transdermally, or rectally (e.g. by the use of suppositories) in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles.

Parenteral includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion technique.

Solid dosage forms for oral administration can include for example capsule, tablets, pills, powders, granules and gel. In such solid dosage forms, the active compounds can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage form can also comprise, as normal practice, additional substance other than inert diluent, e.g., lubricating agent such as magnesium stearate.

Injectable preparations, for example sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing agents, wetting agents and/or suspending agents.

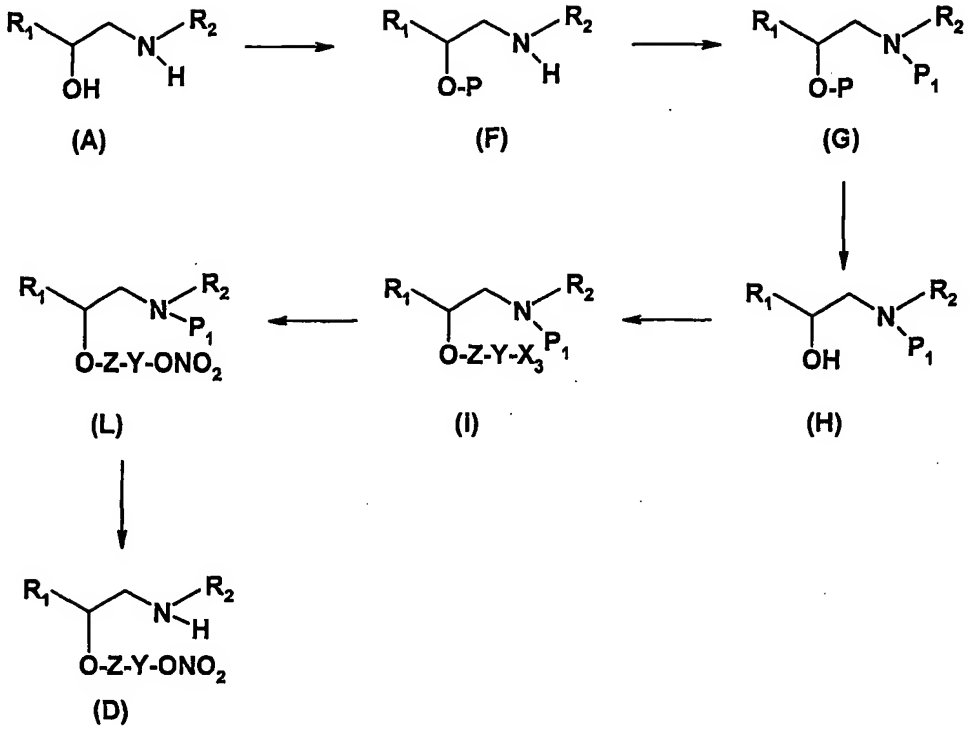
The composition of this invention can further include conventional excipients, i.e., pharmaceutical acceptable organic or inorganic substances which do not deleteriously react with the active compounds.

The doses of β-adrenergic blockers nitrooxyderivatives can be determinated by standard clinique technique and are in the same ranges or less than as described for commercially available compounds as reported in the: Physician's Desk Reference, Medical Economics Company, Inc., Oradell, N.J., 58th Ed., 2004; The pharmacological basis of therapeutics, Goodman and Gilman, J. G. Hardman, L. e. Limbird, 20th Ed.

EXPERIMENTAL: synthesis procedure

The compounds of the invention can be synthesized as shown in Schemes 1 to 6. The compounds of general formula (I) A-(Y-ONO_2)$_s$, defined in Schemes 1-3 as compounds of formula D, wherein s is 1, Y is as above defined and A is a β-adrenergic blocker residue of formula (II), wherein Z is –C(O)- and Z_1 is H, the enantiomers, diastereoisomer and a pharmaceutically acceptable salt thereof, can be prepared as outlined in Schemes 1 -3.

Scheme 1



Compounds of formula (i) wherein R_1, R_2, Z and Y are as above defined, P_1 is an amine protecting group such as tert-butyloxycarbonyl ester (t-Boc) and X_3 is an halogen atom preferably Cl, Br and I, are converted to compounds of formula (L) wherein R_1, R_2, P_1, Z and Y are as above defined, by reaction with $AgNO_3$ in a suitable organic solvent such as acetonitrile, tetrahydrofurane, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature to the boiling temperature of the solvent. The compounds of formula (L) are converted to the compounds of formula (D) by deprotecting the amine group (strong acid, such as HCl in dioxane or trifluoroacetic acid, is used to remove a t-butyl carbamate). Other preferred methods for removing the amine protecting groups are those described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980.

The compounds of formula (H) wherein R_1, R_2, Z, $P_1$and Y are as above defined, are converted to the esters of formula (i) wherein R_1, R_2, Y, Z, X_3 and P_1 are as above defined, by reaction with an appropriate acid (Q1) of formula X_3-Y-COOH wherein Y and X_3 are as above defined. The reaction is generally carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from 0°C to 50°C in presence of a dehydrating agent such as dycyclohexylcarbodiimide DCC or 1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide hydrochloride (EDAC HCl) with a catalyst, such as 4-N,N-dimethylaminopyridine (DMAP).

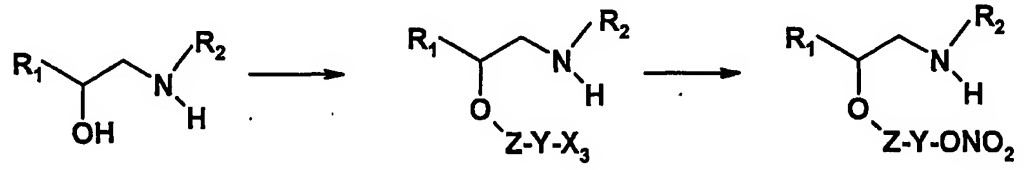
The compounds of formula (H) wherein R_1, R_2 and P_1 are as above defined, can be obtained by deprotecting the hydroxylic group of the compounds of formula (G) wherein R_1, R_2 are as above defined and P is a hydroxylic protecting group such as silyl ethers, such as trimethylsilyl or tert-butyl-dimethylsilyl and those described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980. Fluoride ion is the preferred method for removing silyl ether protecting group.

The compounds of formula (G) wherein R_1, R_2, P and P_1 are as above defined, can be obtained by reacting the compounds of formula (F) wherein R_1, R_2 and P are as above defined with a suitable amine protecting group (P_1) as above described.

The alcohol group of the compounds of formula (A) wherein R_1, R_2 are as above defined, is protected to afford the compounds of formula (F) wherein R_1, R_2 are as above defined Preferred protecting groups for the alcohol moiety are silyl ethers, such as trimethylsilyl or tert-butyl-dimethylsilyl.

The compounds (A) wherein R_1, R_2 are as above defined are commercially available, the acids of formula X_3-Y-COOH wherein X_3 is as above defined, are commercially available.

Scheme 2



(A) (B) (D)

Compounds of formula (B) wherein R_1, R_2, Z, Y are as above defined and X_3 is an halogen atom, such as Cl, Br and I, are converted to compounds of formula (D) wherein R_1, R_2, Z and Y are as above defined, by reaction with $AgNO_3$ in a suitable organic solvent such as acetonitrile, tetrahydrofurane, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature and the boiling temperature of the solvent.

The compounds of formula (B) wherein R_1, R_2, Z, Y and X_3 are as above defined can be obtained by reaction of compounds of formula (A) with an appropriate acid chloride (Q) of formula X_3-Y-C(O)Cl, wherein X_3 is chosen among chlorine, bromine, and Y is as above defined. The reaction of formation of the ester is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, chloroform in

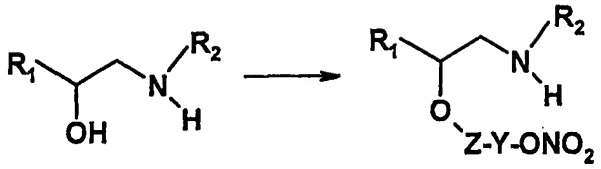
presence of a base as triethylamine, pyridine at a temperature from room temperature and 50°C. The reaction is completed within a time range from 30 minutes to 24 hours.

Alternatively the compounds of formula (B) can be obtained by reaction of a compound of formula (A) with an acid (Q1) of formula X_3-Y-C(O)OH in the presence of a dehydrating agent as dicyclohexylcarbodiimide (DCC) or N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDAC) and a catalyst, such as N,N-dimethylamino pyridine. The reaction is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from 0°C and 50°C. The reaction is completed within a time range from 30 minutes to 36 hours.

The compounds of formula (Q1), where X_3 is an halogen atom are commercially available or can be obtained from the corresponding commercially available hydroxyl acid by well known reactions, for example by reaction with thionyl or oxalyl chloride, halides of P^{III} or P^{V} in solvents inert such as toluene, chloroform, DMF, etc.

The compounds (A) wherein R_1, R_2 are as above defined are commercially available.

Scheme 3

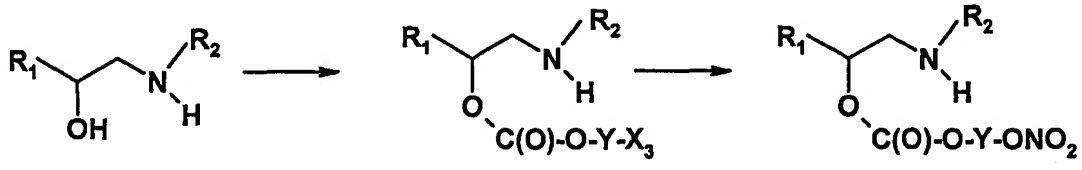


(A) (D)

Alternatively the compounds of formula (D) can be obtained as described below. The compounds of formula A are converted to the ester (D) by reaction of the alcohol group with a nitrooxyderivative, containing activated acylating group, of formula $Cl(O)C\text{-}Y\text{-}ONO_2$. The nitrooxy compounds can be obtained from the corresponding alcohols of formula Cl(O)C-Y-OH by reaction with nitric acid and acetic anhydride in a temperature range from –50°C to 0°C or from the corresponding halogen derivatives of formula Cl(O)C-Y-Hal by reaction with silver nitrate in the presence of an inert solvent such as acetonitrile, tetrahydrofurane. A silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, a temperature from the boiling temperature and room temperature. The reaction is completed within a time range from 30 minutes to 3 days.

The compounds of general formula (I) $A\text{-}(Y\text{-}ONO_2)_s$, defined in Scheme 4 as compounds of formula (D1), wherein s is 1, Y is as above defined and A is a β-adrenergic blocker residue of formula (II), wherein Z is -C(O)O- and Z_1 is H, the enantiomers, diastereoisomer and a pharmaceutically acceptable salt thereof, can be prepared as outlined in Scheme 4.

Scheme 4



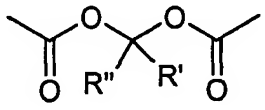
(A) (B1) (D1)

The compounds of formula (B1) wherein R_1, R_2, Y are as above defined and X_3 is an halogen atom, such as Cl, Br and I, are converted to compounds of formula (D1) wherein R_1, R_2, and Y are as above defined, by reaction with $AgNO_3$ in a suitable organic solvent such as acetonitrile, tetrahydrofurane, a silver nitrate molar excess is preferably used and

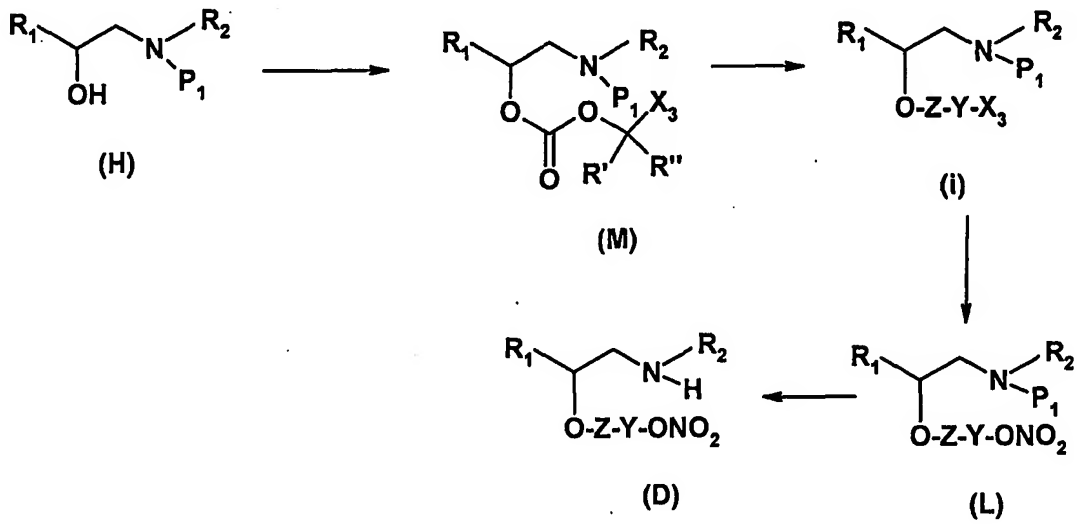
the reaction is carried out, in the dark, at a temperature from room temperature and the boiling temperature of the solvent.

The compounds of formula (A) wherein R_1 and R_2 are as above defined are converted to the compounds (B1) by reaction with an appropriate compound (Q2) having formula X_3-Y-OC(O)Cl wherein X_3 is Cl, Br or I, and Y is as defined above. The reaction is generally carried out in presence of a base in an aprotic polar or non-polar solvent such as THF or CH_2Cl_2 at temperatures range between 0°-65°C or in a double phase system H_2O/Et_2O at temperatures range between 20°- 40°C.

The compounds of formula (Q2) are commercially available or can be obtained from the corresponding alcohols by reaction with triphosgene in presence of an organic base.

The compounds of general formula (I) A-(Y-ONO_2)$_s$, defined in Scheme 5 as compounds of formula (D), wherein s is 1, Y is as above defined and A is a β-adrenergic blocker residue of formula (II), wherein Z is  wherein R' and R" are as above defined and Z_1 is H, the enantiomers, diastereoisomer and a pharmaceutically acceptable salts thereof, may be prepared as outlined in Scheme 5:

Scheme 5



The compounds of formula (i) wherein R_1, R_2, Z and Y are as above defined, P_1 is an amine protecting group such as tert-butyloxycarbonyl ester (t-Boc) and X_3 is an halogen atom such as Cl, Br and I, are converted to compounds of formula (L) wherein R_1, R_2, P_1, Z and Y are as above defined, by reaction with $AgNO_3$ in a suitable organic solvent such as acetonitrile, tetrahydrofurane, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature and the

boiling temperature of the solvent. The compounds of formula (L) are converted to the compounds of formula (D) by deprotecting the amine group (strong acid, such as HCl in dioxane or trifluoroacetic acid, is used to remove a t-butyl carbamate). Other preferred methods for removing the amine protecting groups are those described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980.

The compounds of formula (i) wherein R_1, R_2, Y, X_3, Z and P_1 are as above defined, can be obtained by reacting the compounds of formula (M) wherein R_1, R_2, P_1, R', R" and X_3 are as above defined, with an acid (Q1) of formula X_3-Y-COOH wherein X_3 is an halogen atom and Y is as above defined. The reaction is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from 0°C and 50°C in the presence of a dehydrating agent such as dycyclohexylcarbodiimide DCC or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC HCl) with a catalyst, such as 4-N,N-dimethylaminopyridine (DMAP).

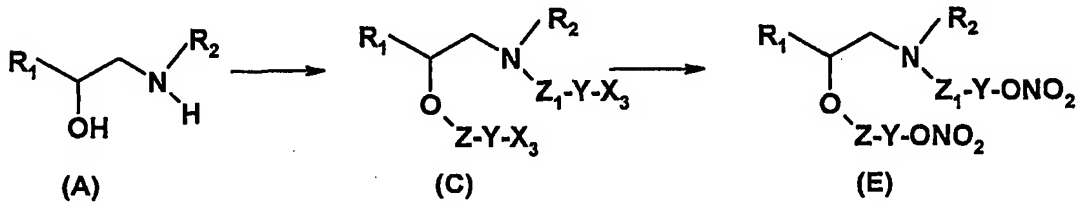
The reaction is complete within a time range from 30 minutes to 24 hours.

The compounds of formula (M) wherein R_1, R_2, P_1, R', R" and X_3 are as above defined, can be obtained by reacting compounds the of formula (H) with an acyl compound (S) of formula X_3-C(R')(R")-OC(O)X_3 wherein X_3 is an halogen atom. The reaction is carried out in presence of an organic or inorganic base in a polar solvent as DMF, THF, acetonitrile at a temperature in the range from –5°C to 60°C or in a double phase system according to methods well known in the literature.

The amine group of the compounds (A) is protected to afford the compounds of formula (H) wherein P_1 is a suitable amine protecting group such as tert-butyloxycarbonyl ester (t-Boc) The compounds (S) are commercially available.

The compounds of general formula (I) A-(Y-ONO_2)$_s$, defined in Scheme 6 as compounds of formula (E), wherein s is 2, Y is as above defined and A is a β-adrenergic blocker residue of formula (II), wherein Z_1 and Z are –C(O)-, the enantiomers, diastereoisomer and a pharmaceutically acceptable salt thereof, can be synthesized as shown in Scheme 6.

Scheme 6



Compound of formula (C) wherein R_1, R_2, Z, Z_1 and Y are as above defined and X_3 is an halogen atom, such as Cl, Br and I, are converted to compounds of formula (E) wherein R_1, R_2, Z and Y are as above defined, by reaction with $AgNO_3$ in a suitable organic solvent such as acetonitrile, tetrahydrofurane, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature and the boiling temperature of the solvent.

The compounds of formula (C) wherein R_1, R_2, Z, Z_1, Y and X_3 are as above defined can be obtained by reaction of compounds of formula (A) with an appropriate acid chloride (Q) of formula X_3-Y-C(O)Cl, wherein X_3 is chosen among chlorine, bromine, and Y is as above defined. The reaction is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, chloroform in presence of a base as triethylamine, pyridine at a temperature from room temperature and 50°C. The reaction is completed within a time range from 30 minutes to 24 hours.

Alternatively the compounds of formula (C) can be obtained by reaction of compounds of formula (A) with an acid (Q1) of formula X_3-Y-COOH in the presence of a dehydrating agent such as dicyclohexylcarbodiimide (DCC) or N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDAC) and a catalytic amount of N,N-dimethylamino pyridine. The reaction is carried out in an inert organic solvent such as as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from 0°C and 50°C. The reaction is completed within a time range from 30 minutes to 36 hours.

The compounds of formula (Q1), where X_3 is an halogen atom are commercially available or can be obtained from the corresponding commercially available hydroxyl acids by well known reactions, for example by reaction with thionyl or oxalyl chloride, halides of P^{III} or P^{V} in solvents inert such as toluene, chloroform, DMF, etc.

The compounds (A) wherein R_1, R_2 are as above defined are commercially available.

The compounds of formula (D) can also be obtained as described below. The compounds of formula A are converted to the compounds (E) by reaction with a nitrooxy derivative of formula Cl(O)C-Y-ONO_2 containing an activated acylating group.

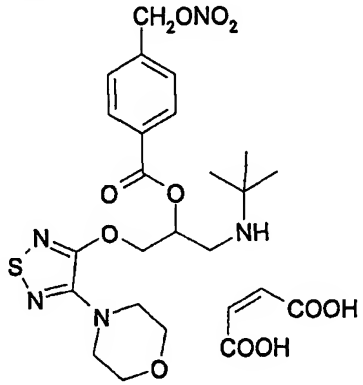
The nitrooxy-compounds can be obtained from the corresponding alcohols of formula Cl(O)C-Y-OH by reaction with nitric acid and acetic anhydride in a temperature range from –50°C to 0°C or from the corresponding halogen derivatives of formula Cl(O)C-Y-Hal by reaction with silver nitrate in the presence of an inert solvent such as acetonitrile, tetrahydrofurane. A silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, a temperature from the boiling temperature and room temperature. The reaction is completed within a time range from 30 minutes to 3 days.

EXAMPLES

The following non-limiting examples further describe and enable of ordinary skilled in the art to make and use the present invention.

Example 1

4-(Nitrooxymethyl)benzoic acid (S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanoate maleate salt



1a. 4-(Chloromethyl)benzoic acid (S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanoate

To a solution of timolol (3.5g, 11mmol) in chloroform (200ml) 4-chloromethyl benzoic acid (1.9g, 11mmol), EDAC (3.16g, 16.5mmol) and N,N-dimethylaminopyridine (catalytic amount) were added. The reaction was stirred for 12 hours at room temperature. The solution was washed with water, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with chloroform/isopropanol 10/0.5 to give the title compound 3g as a white powder.

1b. 4-(Nitrooxymethyl)benzoic acid (S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanoate

A solution of the product of example 1a (1g, 2.1mmol) and silver nitrate (0.71g, 4.21mmol) in acetonitrile (50ml) was stirred at 60°C, in the dark, for 36 hours. The precipitated (silver salts) was removed by filtration and the solvent was evaporated under vacuum. The residue was treated with chloroform and water. The organic layer was dried over sodium sulfate and the solvent was evaporeted. The residue was purified by flash chromatography, eluting with chloroform/isopropanol 10/0.5 to give the title compound 0.6g as white powder.

1c. 4-(Nitrooxymethyl)benzoic acid (S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanoate maleate salt

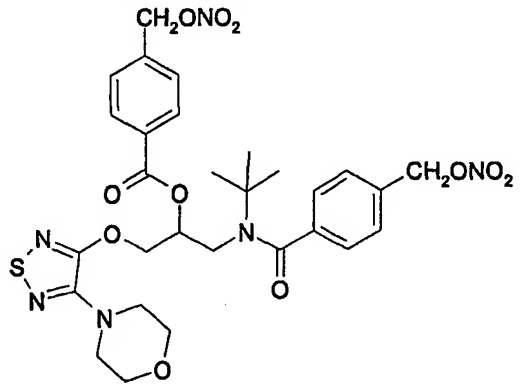
To a solution of the product of the example 1b (0.6g, 1.2mmol) in acetone (100ml) maleic acid (0.14g, 1.2mmol) was added. The reaction was stirred at room temperature for 1 hours. The precipitated was filtered, washed with acetone and dried under vacuum to afford the title compound 0.6g as a white powder.

M.p.= 160°C

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.99 (2H,d); 7.42 (2H,d); 5.93 (2H,s); 5.87 (1H,m); 5.46 (2H,s); 4.82 (1H,dd); 4.71 (1H,dd); 3.73 (4H,m); 3.44 (4H,m);1.49 (9H,s).

Example 2

4-(Nitrooxymethyl)benzoic acid (S)-1-[(1,1-dimethylethyl)[(4-nitrooxymethyl)benzoyl] amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanoate



2a. 4-(Chloromethyl)benzoic acid (S)-1-[(1,1-dimethylethyl)[(4-chloromethyl)benzoyl] amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanoate

To a solution of timolol hydrocloride (8g, 22,66mmol) in chloroform (130ml) a mixture of 4-chloromethyl benzoylchloride (4,28g, 22,66mmol) and triethylamine (6.2ml, 44.66mmol) in chloroform (70ml) was added dropwise. The reaction was stirred for 24 hours at room temperature. The solution was treated with water and diethyl ether, the organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with chloroform/isopropanol 10/0.3 to give the title compound 3g as powder.

2b. 4-(Nitrooxymethyl)benzoic acid (S)-1-[(1,1-dimethylethyl)[(4-nitrooxymethyl)benzoyl] amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanoate

A solution of the product of example 2a (1.5g, 2.4mmol) and silver nitrate (1.23g, 7.2mmol) in acetonitrile (100ml) was stirred at 60°C, in the dark, for 36 hours. The precipitated (silver salts) was removed by filtration and the filtrate was concentrated. The residue was treated with chloroform and water and the organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by

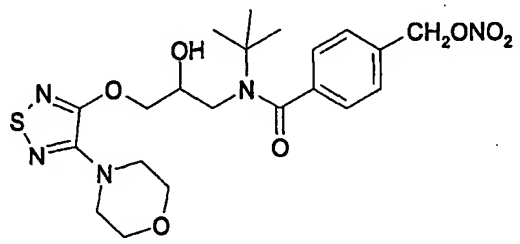
flash chromatography eluting with chloroform/isopropanol 10/0.2 to give the title product 0.95g as a yellow powder.

M.p.= 44-46°C

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.95 (2H,d); 7.50 (2H,d); 7.38(4H,s); 5.79 (1H,m); 5.75(2H,s), 5.74 (2H,s); 4.50 (1H,dd); 4.30 (1H,dd); 3.95 (1H,dd); 3.85 (1H,dd); 3.59 (4H,m); 3.34 (4H,m); 1.60 (9H,s).

Example 3

(S)-1-[(1,1-dimethylethyl)[(4-nitrooxymethyl)benzoyl] amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol



3a. (S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propan-1- tert-butyldimethylsilylether

To a solution of timolol (2g, 6,32mmol) in N,N-dimethylformamide (10ml) tert-butyldimethylsilylchloride (1,15g, 7,58mmol) and imidazole (1g, 15,8mmol) were added. The reaction was stirred for 2 hours at room temperature. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography eluting with chloroform/isopropanol 10/0.3 to give the title compound 1,5g.

3b. (S)-1-[(1,1-dimethylethyl)[(4-chloromethyl)benzoyl]amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propan-1- tert-butyldimethylsilylether

To a solution of the product of the example 3a (0,7g, 1,62mmol) in chloroform (50ml) 4-chloromethyl benzoylchloride (0,46g, 2,44mmol) and triethylamine (0,39ml, 2,44mmol) were added. The reaction was stirred for 24 hours at room temperature. The solution was treated with water and diethyl ether, the organic layers were dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 7/3 to give the title product (0,7g).

3c. (S)-1-[(1,1-dimethylethyl)[(4-chloromethyl)benzoyl] amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol

To a solution of the product of example 3b (0,6g, 1,03mmol) in tetrahydrofuran (50ml) cooled at 0°C, a solution of tetrabutylamonium floride in tetrahydrofuran 1M (0,54ml, 2,05mmol) was added. The reaction was stirred for 30 minutes at room temperature. The

solution was concentrated under reduced pressure and the residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 1/1 to give the title product 0,2g.

3d. (S)-1-[(1,1-dimethylethyl)[(4-nitrooxymethyl)benzoyl] amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol

A solution of the product of example 3c (0,15g, 0,32mmol) and silver nitrate (0,11g, 0,64mmol) in acetonitrile (50ml) was stirred at 65°C, in the dark, for 32 hours. The precipitated (silver salts) was removed by filtration and the filtrate concentrate. The residue was treated with methylene chloride and water and the organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 45/65 to afford the title compound 0.65g as a white powder.

M.p.= 50-54°C

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.40 (4H,s); 5.44 (2H,s); 4.33-4.18(3H,m), 3.79 (4H,dd); 3.64-3.50 ((2H,m); 4.46 (4H,dd); 3.00 (1H,s); 1.53 (9H,s).

Example 4

Measurements of cGMP in rat PC12 cell line.

cGMP contributes to the function and interaction of several vascular cell types and its dysfunction is involved in major cardiovascular diseases such as hypertension, diabetic complications, atherosclerosis, and tissue infarction. Therefore the extent of cGMP formation elicited by the compounds of the inventions was evaluated in the rat pheochromocytoma (PC12) cell line.

Tested compounds

1) Timolol (parent compound)

2) 4-(Nitrooxymethyl)benzoic acid (S)-1-[(1,1-dimethylethyl)[(4-nitrooxymethyl)benzoyl] amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanoate (compound of example 1)

3) 4-(Nitrooxymethyl)benzoic acid (S)-1-[(1,1-dimethylethyl)[(4-nitrooxymethyl)benzoyl] amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanoate (compound of example 2)

4) (S)-1-[(1,1-dimethylethyl)[(4-nitrooxymethyl)benzoyl]amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol (compound of example 3)

Method

Cells were maintained at 37°C in DMEM medium enriched with 10% horse serum and 5% foetal bovine serum under 5% CO_2 atmosphere. At the time of experiments the cells were washed once with Hank's Balanced Salt Solution (HBSS) supplemented with

0.05% ascorbic acid and preincubated in the same buffer for 10 min in a floating water bath. After the preincubation step, cells were exposed for additional 45 min to either control conditions or increasing concentrations of test compounds ranging from 0.1 to 25 μM, in the presence of the phosphodiesterase inhibitor, IBMX (100 μM) and the NO-independent activator of soluble guanylyl cyclase, YC-1 (20 μM). The reaction was terminated by the removal of the incubating buffer and consecutive addition of 100 μl of absolute ethanol. The organic extracts were then evaporated to dryness and the residues dissolved in aqueous buffer for quantitative determination of intracellular cGMP levels using the cGMP enzyme immunoassay kit .

The obtained results reported in Table 1 are expressed as EC_{50} (μM) and efficacy Emax (% of vehicle). As shown in the table the nitroderivatives of timolol elicited consistent increase of intracellular cGMP formation in PC12 cell line. Conversely, this effect was not shared by the parent compound .

Table 1. Effects of nitroxyderivatives of timolol and ann of timolol on cGMP formation in PC12 cells

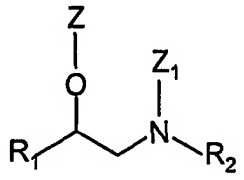
Compound	**EC_{50} (μM)**	**E_{max} (% of vehicle)**
Timolol	Not effective	Not effective
Compound of example 2	1.3	480
Compound of example 1	12.6	796
Compound of example 3	18.5	866

CLAIMS

1. A compound of general formula (I) A-(Y-ONO_2)$_s$ and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof, wherein

s is an integer equal to 1 or 2;

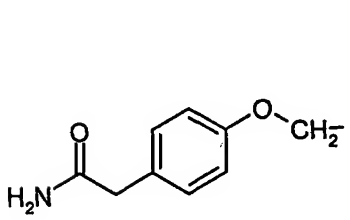
A is selected from the following β-adrenergic blockers residues of formula (II):



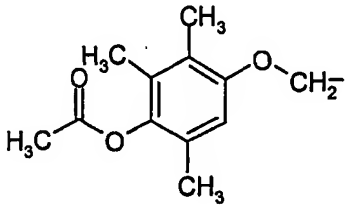
(II)

wherein

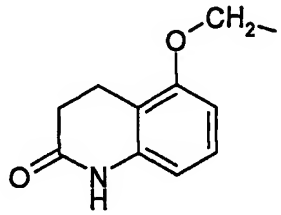
R_1 is selected from the group consisting of:



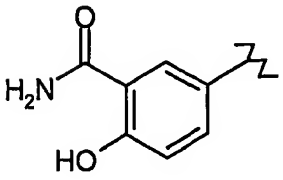
(IIo)



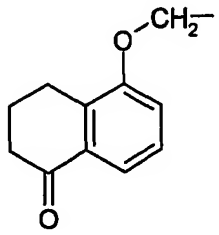
(IIp)



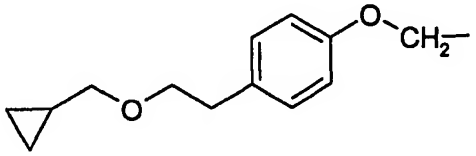
(IIq)



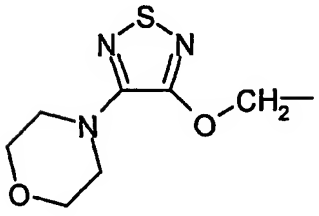
(IIr)



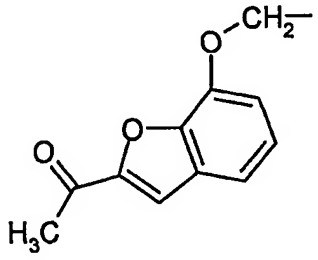
(IIs)



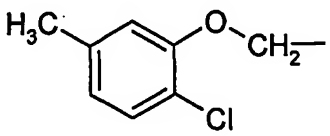
(IIt)



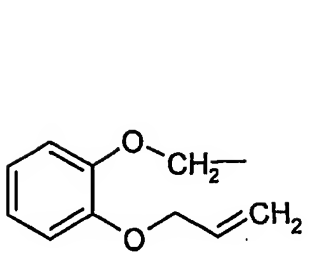
(IIu)



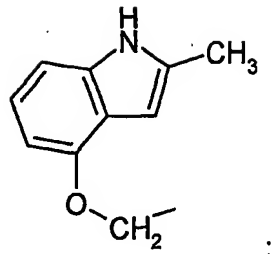
(IIv)



(IIw)

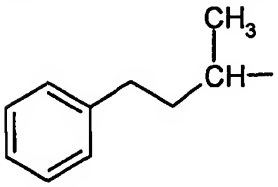


(IIy)



(IIz)

R_2 is selected from the group consisting of: $-CH(CH_3)_2$, $-C(CH_3)_3$ or



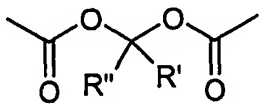
(IIIc)

when the radical R_1 has chosen from the formulae (IIo), (IIp), (IIt), (IIu), (IIv), (IIy) or (IIz), R_2 is $-CH(CH_3)_2$;

when the radical R_1 has chosen from the formulae (IIq), (IIs) or (IIw), R_2 is $-C(CH_3)_3$;

when the radical R_1 is (IIr), R_2 is (IIIc);

Z is H or is a group capable of binding Y selected from the group consisting of: –C(O)-, –C(O)O- or



wherein R' and R" are the same or different, and are H or straight or branched C_1-C_4 alkyl;

Z_1 is H or a –C(O)-group capable of binding Y;

with the proviso that when s of formula (I) is 1 Z or Z_1 is H;

Y is a bivalent radical having the following meaning:

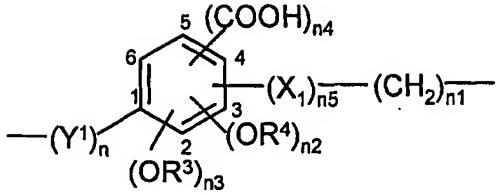
a)

- straight or branched C_1-C_{20} alkylene being optionally substituted with one or more of the substituents selected from the group consisting of halogen atoms, hydroxy, $–ONO_2$ or T, wherein T is $–OC(O)(C_1$-C_{10}alkyl)-ONO_2, $–O(C_1$-C_{10}alkyl)-ONO_2;

b)

- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T_1, wherein T_1 is straight or branched alkyl with from 1 to 10 carbon atoms;

c)



(IV)

wherein:

n is an integer from 0 to 20, and n1 is an integer from 1 to 20;

n2, n3, n4 and n5 are integers equal or different from each other, equal to 0 or 1;

R^3 and R^4 are independently selected from H or CH_3;

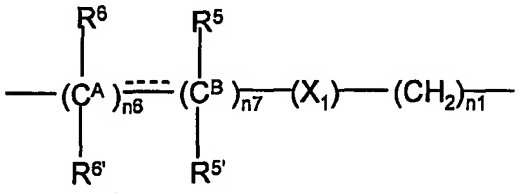
Y^1 is $-CH_2-$ or $-(CH_2)_{na}-CH=CH-$ wherein na is an integer from 0 to 20;

X_1 is $-WC(O)-$ or $-C(O)W-$, wherein W is oxygen, sulfur or NH;

with the proviso that:

- when s of formula (I) is 1, Z is –(CO)- and in formula (IV) of the bivalent radical Y n2, n3, n4, n5 are equal to 0 then n is 0 and n1 is 1;
- when s of formula (I) is 1, Z is –(CO)- and in formula (IV) of the bivalent radical Y n2, n3, n5 are equal to 0, n4 is 1 then n and n1 are different to 1;

d)



(V)

wherein:

n1 is an integer from 1 to 20;

X_1 is $-WC(O)-$ or $-C(O)W-$, wherein W is oxygen, sulfur or NH;

n6 is an integer from 1 to 20,

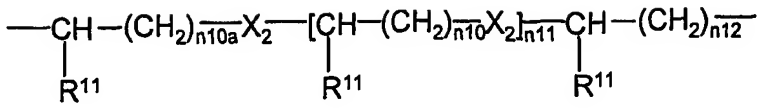
n7 is an integer from 0 to 20,

R^5 and $R^{5'}$ R^6 and $R^{6'}$ are independently selected from the group consisting of H, CH_3, OH, NH_2, $NHCOCH_3$, COOH, CH_2SH and $C(CH_3)_2SH$; when the bond between the C^A and C^B carbons is a double bond R^5 and R^6 or $R^{6'}$ and $R^{5'}$ are absent;

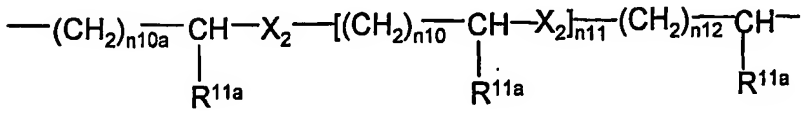
with the proviso that when Y is selected from the bivalent radicals mentioned under c)-d), the $-ONO_2$ group is linked to a $-(CH_2)_{n1}-$ group;

with the proviso that when s of formula (I) is 1 and Z is –(CO)- then the bivalent radical Y has not the meanings under a), b) and d);

e)



(VI)



(VII)

wherein X_2 is O or S,

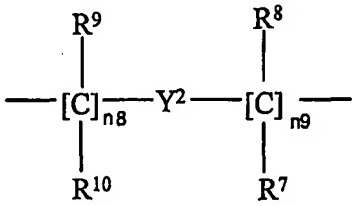
n10a, n10 and n12 are integer independently selected from 0 to 20,

n11 is an integer from 0 to 6,

R^{11} is H, CH_3 or nitrooxy group;

with the proviso that when in formula (I) s is 1, in formula (II) Z is –(CO)-, in formula (VI) of the bivalent radical Y n10a, n10, n12 are equal to 1 then X can not be an oxygen atom;

f)



(VIII)

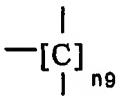
wherein:

n8 is an integer from 0 to 10;

n9 is an integer from 1 to 10;

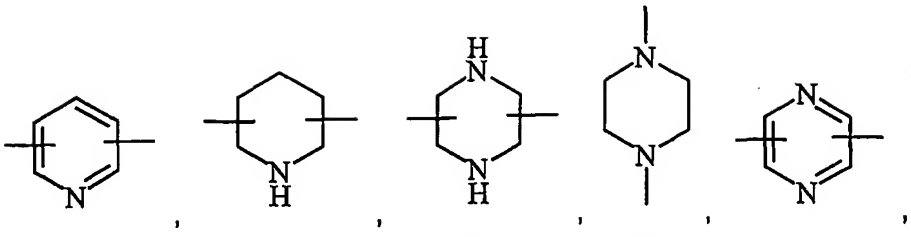
R^9, R^{10}, R^8, R^7 are the same or different, and are H or straight or branched C_1-C_4 alkyl;

wherein the $–ONO_2$ group is linked to

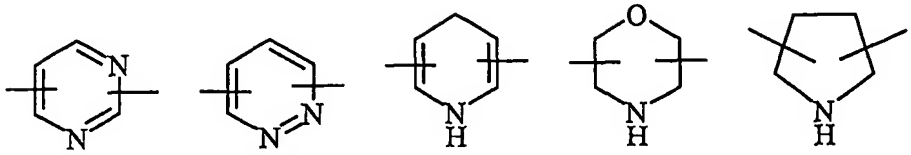


wherein n9 is as defined above;

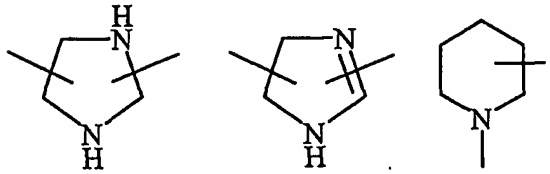
Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur, and is selected from the group consisting of:



(Y1) (Y2) (Y3) (Y4) (Y5)



(Y6) (Y7) (Y8) (Y9) (Y10)

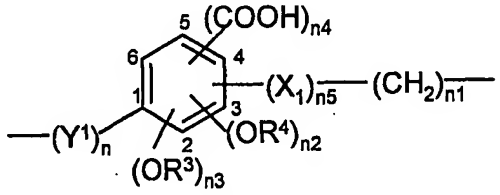


(Y11) (Y12) (Y13)

2. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 1 wherein
s is equal to 1 and Z_1 is H.

3. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 2 wherein Z is –C(O)-.

4. A compound and enantiomers and diastereoisomers and pharmaceutically acceptable salts thereof according to claim 3 wherein
Y is

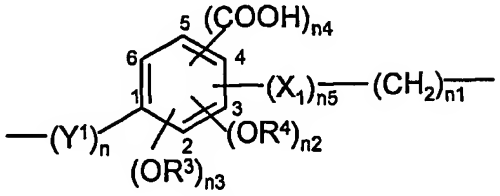


(IV)

wherein
n, n2, n3, n4 and n5 are equal to 0
n1 is an integer equal to 1;

5. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 3 wherein

Y is



(IV)

wherein

n, n2, n5 are 1,

n3 and n4 are equal to 0,

n1 is an integer from 1 to 10,

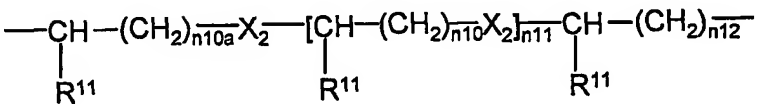
Y^1 is $-(CH_2)_{na}$-CH=CH- wherein na is 0,

X_1 is –WC(O)- wherein W is oxygen and X_1 is bound to the phenyl ring through the $[C]_4$,

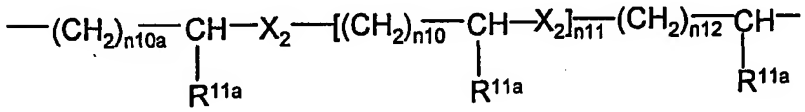
R^4 is CH_3 and the (OR^4) group is bound to the phenyl ring through the $[C]_3$.

6. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 3 wherein

Y is



(VI)



(VII)

wherein

X_2 is O or S,

n10a, n10 and n12 are integers independently selected from 2 to 20;

n11 is an integer from 0 to 6;

R^{11} is H, CH_3 or a nitrooxy group;

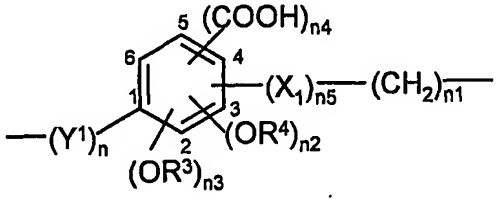
R^{11a} is CH_3 or a nitrooxy group.

7. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 2 wherein Z is –C(O)O-.

8. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 7 wherein
Y is a straight or branched C_1-C_{20} alkylene being optionally substituted with one or more of the substituents selected from the group consisting of halogen atoms, hydroxy, $–ONO_2$ or T, wherein T is $–OC(O)(C_1$-C_{10}alkyl)-ONO_2, $–O(C_1$-C_{10}alkyl)-ONO_2.

9. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 8 wherein
Y is a straight or branched C_1-C_{10} alkylene.

10. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 7 wherein
Y is



(IV)

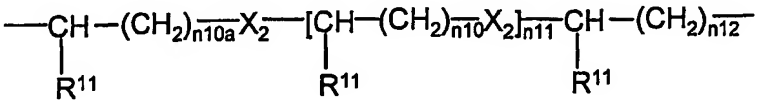
wherein
n is an integer from 0 to 20,
n1 is an integer from 1 to 20;
n2, n3, n4 and n5 are integers equal or different from each other, equal to 0 or 1;
R^3 and R^4 are independently selected from H or CH_3;
Y^1 is $–CH_2$- or $–(CH_2)_{na}$-CH=CH- wherein na is an integer from 0 to 20;
X_1 is –WC(O)- or –C(O)W-, wherein W is oxygen, sulfur or NH.

11. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 10 wherein
n2, n3, n4, n5 are equal to 0,
n1 is 1,
n is an integer from 0 to 10,

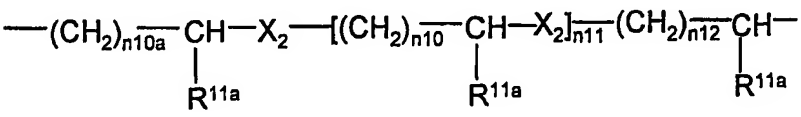
Y^1 is CH_2.

12. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 7 wherein

Y is



(VI)



(VII)

wherein

X_2 is O or S,

n10a, n10 and n12 are integers independently selected from 0 to 20;

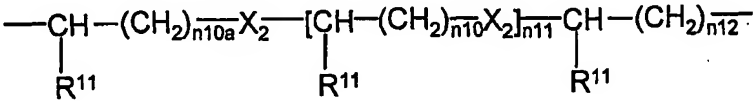
n11 is an integer from 0 to 6;

R^{11} is H, CH_3 or a nitrooxy group;

R^{11a} is CH_3 or a nitrooxy group.

13. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 12 wherein

Y is



(VI)

wherein

X_2 is O or S,

n10a and n11 are 0,

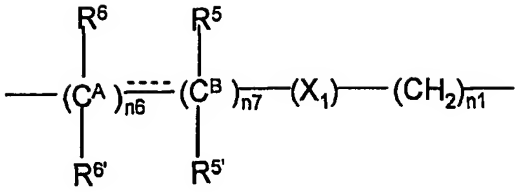
n12 is 1, and

R^{11} is H;

wherein the $-ONO_2$ group is bound to the $-(CH_2)_{n12}-$ group.

14. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 7 wherein

Y is



(V)

wherein:

n1 is an integer from 1 to 20;

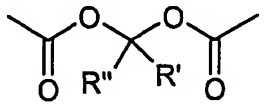
X_1 is –WC(O)- or a –C(O)W-, wherein W is oxygen, sulfur or NH.

n6 is an integer from 1 to 20,

n7 is an integer from 0 to 20,

R^5 and $R^{5'}$ R^6 and $R^{6'}$ are independently selected from the group consisting of: H, CH_3, OH, NH_2, $NHCOCH_3$, COOH, CH_2SH and $C(CH_3)_2SH$; when the bond between the C^A and C^B carbons is a double bond R^5 and R^6 or $R^{6'}$ and $R^{5'}$ are absent.

15. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claims 2 wherein Z is



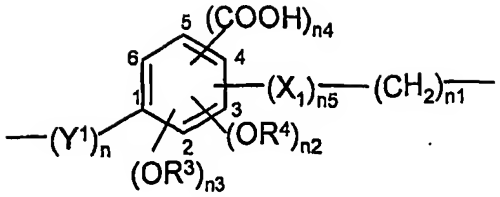
16. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 15 wherein

Y is a straight or branched C_1-C_{20} alkylene being optionally substituted with one or more of the substituents selected from the group consisting of halogen atoms, hydroxy, $–ONO_2$ or T, wherein T is $–OC(O)(C_1$-C_{10}alkyl)-ONO_2, $–O(C_1$-C_{10}alkyl)-ONO_2.

17. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 16 wherein Y is a straight or branched C_1-C_{10} alkylene.

18. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 15 wherein

Y is



(IV)

wherein

n is an integer from 0 to 20,

n1 is an integer from 1 to 20,

n2, n3, n4 and n5 are integers equal or different from each other, equal to 0 or 1;

R^3 and R^4 are independently selected from H or CH_3;

Y^1 is $-CH_2-$ or $-(CH_2)_{na}-CH=CH-$ wherein na is an integer from 0 to 20;

X_1 is –WC(O)- or –C(O)W-, wherein W is oxygen, sulfur or NH.

19. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 18 wherein

n2, n3, n4, n5 are equal to 0,

n1 is 1,

n is an integer from 0 to 10,

Y^1 is CH_2.

20. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 1 wherein Z and Z_1 are –C(O)-.

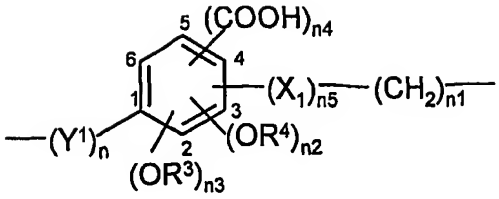
21. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 20 wherein

Y is a straight or branched C_1-C_{20} alkylene being optionally substituted with one or more of the substituents selected from the group consisting of halogen atoms, hydroxy, $-ONO_2$ or T, wherein T is $-OC(O)(C_1-C_{10}alkyl)-ONO_2$, $-O(C_1-C_{10}alkyl)-ONO_2$.

22. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 21 wherein Y is a straight or branched C_1-C_{10} alkylene.

23. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 20 wherein

Y is



(IV)

wherein

n is an integer from 0 to 20,

n1 is an integer from 1 to 20,

n2, n3, n4 and n5 are integers equal or different from each other, equal to 0 or 1,

R^3 and R^4 are independently selected from H or CH_3;

Y^1 is $-CH_2-$ or $-(CH_2)_{na}-CH=CH-$ wherein na is an integer from 0 to 20;

X_1 is –WC(O)- or –C(O)W-, wherein W is oxygen, sulfur or NH.

24. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 23 wherein

n2, n3, n4, n5 are equal to 0,

n1 is 1,

n is an integer from 0 to 10,

Y^1 is CH_2.

25. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 23 wherein

n, n2, n5 are 1,

n3 and n4 are equal to 0,

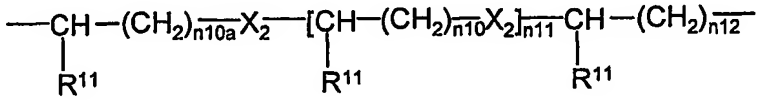
n1 is an integer from 1 to 10,

Y^1 is $-(CH_2)_{na}-CH=CH-$ wherein na is 0,

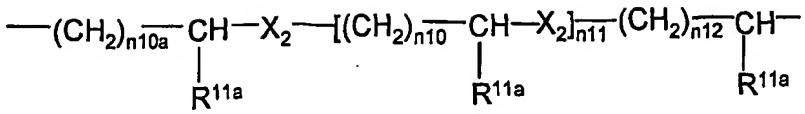
X_1 is –WC(O)- wherein W is oxygen and X_1 is bound to the phenyl ring through the $[C]_4$, R^4 is CH_3 and the group (OR^4) is bound to the phenyl ring through the $[C]_3$.

26. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 20 wherein

Y is



(VI)



(VII)

wherein

X_2 is O or S,

n10a, n10 and n12 are integers independently selected from 0 to 20;

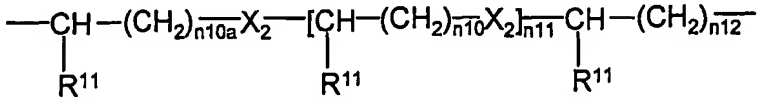
n11 is an integer from 0 to 6;

R^{11} is H, CH_3 or a nitrooxy group;

R^{11a} is CH_3 or a nitrooxy group.

27. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 26 wherein

Y is



(VI)

wherein

X_2 is O or S,

n10a and n11 are 0,

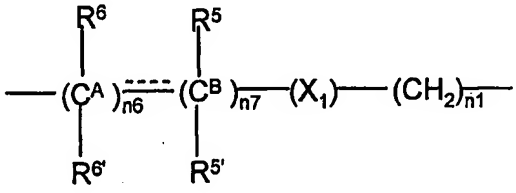
n12 is 1,

R^{11} is H;

wherein the $-ONO_2$ group is bound to the $-(CH_2)_{n12}-$ group.

28. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 20 wherein

Y is



(V)

wherein:

n1 is an integer from 1 to 20;

X_1 is –WC(O)- or a –C(O)W-, wherein W is oxygen, sulfur or NH.

n6 is an integer from 1 to 20,

n7 is an integer from 0 to 20,

R^5 and $R^{5'}$ R^6 and $R^{6'}$ are independently selected from the group consisting of:

H, CH_3, OH, NH_2, $NHCOCH_3$, COOH, CH_2SH and $C(CH_3)_2SH$;

when the bond between the C^A and C^B carbons is a double bond R^5 and R^6 or $R^{6'}$ and $R^{5'}$ are absent.

29. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 28 wherein

n1 is an integer from 1 to 10,

n6 and n7 are 1;

X_1 is –WC(O)- wherein W is sulfur,

R^5, $R^{5'}$ and $R^{6'}$ are H,

R^6 is $NHCOCH_3$,

with the proviso that the $-ONO_2$ group is bound to the $-(CH_2)_{n1}-$ group.

30. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 1 wherein s is 1, Z is H and Z_1 are –C(O)-.

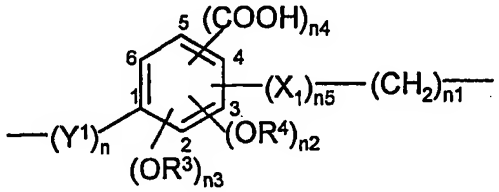
31. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 30 wherein

Y is a straight or branched C_1-C_{20} alkylene being optionally substituted with one or more of the substituents selected from the group consisting of halogen atoms, hydroxy, $-ONO_2$ or T, wherein T is $-OC(O)(C_1$-C_{10}alkyl)-ONO_2, $-O(C_1$-C_{10}alkyl)-ONO_2.

32. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 31 wherein Y is a straight or branched C_1-C_{10} alkylene.

33. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 30 wherein

Y is



(IV)

wherein

n is an integer from 0 to 20,

n1 is an integer from 1 to 20;

n2, n3, n4 and n5 are integers equal or different from each other, equal to 0 or 1;

R^3 and R^4 are independently selected from H or CH_3;

Y^1 is $-CH_2-$ or $-(CH_2)_{na}-CH=CH-$ wherein na is an integer from 0 to 20;

X_1 is –WC(O)- or –C(O)W-, wherein W is oxygen, sulfur or NH.

34. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 33 wherein

n2, n3, n4, n5 are equal to 0,

n1 is 1,

n is an integer from 0 to 10

Y^1 is CH_2.

35. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 33 wherein

n, n2, n5 are 1,

n3 and n4 are equal to 0,

n1 is an integer from 1 to 10,

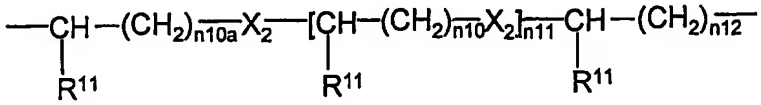
Y^1 is $-(CH_2)_{na}-CH=CH-$ wherein na is 0,

X_1 is –WC(O)-, wherein W is oxygen and X_1 is bound to the phenyl ring through the $[C]_4$,

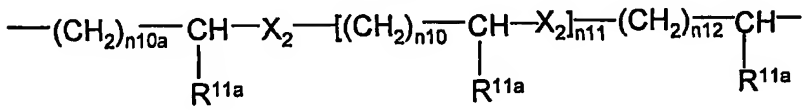
R^4 is CH_3 and the group (OR^4) is bound to the phenyl ring through the $[C]_3$.

36. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 30 wherein

Y is



(VI)



(VII)

wherein

X_2 is O or S,

n10a, n10 and n12 are integers independently selected from 0 to 20;

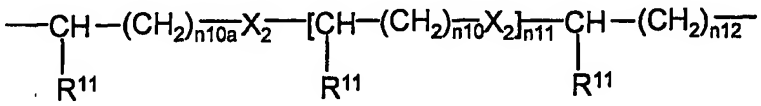
n11 is an integer from 0 to 6;

R^{11} is H, CH_3 or a nitrooxy group;

R^{11a} is CH_3 or a nitrooxy group.

37. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 36 wherein

Y is



(VI)

wherein

X_2 is O or S,

n10a and n11 are 0,

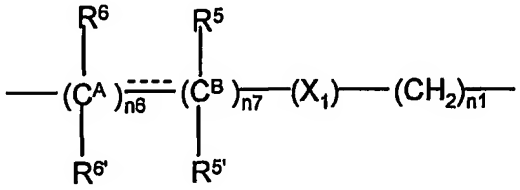
n12 is 1,

R^{11} is H,

wherein the $-ONO_2$ group is bound to the $-(CH_2)_{n12}-$ group.

38. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 30 wherein

Y is



(V)

wherein:

n1 is an integer from 1 to 20;

X_1 is –WC(O)- or a –C(O)W-, wherein W is oxygen, sulfur or NH.

n6 is an integer from 1 to 20,

n7 is an integer from 0 to 20,

R^5 and $R^{5'}$ R^6 and $R^{6'}$ are independently selected from the group consisting of: H, CH_3, OH, NH_2, $NHCOCH_3$, COOH, CH_2SH and $C(CH_3)_2SH$;

when the bond between the C^A and C^B carbons is a double bond R^5 and R^6 or $R^{6'}$ and $R^{5'}$ are absent.

39. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 38 wherein

n1 is an integer from 1 to 10,

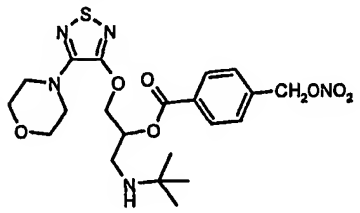
n6 and n7 are 1;

X_1 is –WC(O)- wherein W is sulfur;

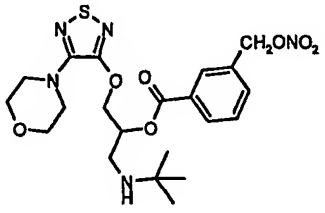
R^5, $R^{5'}$ and $R^{6'}$are H, R^6 is $NHCOCH_3$;

with the proviso that the $-ONO_2$ group is bound to the $-(CH_2)_{n1}-$.

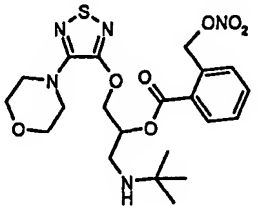
40. Compounds and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 3 and claim 4 wherein the compounds are:



(1)

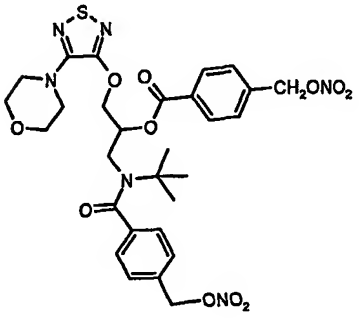


(2)

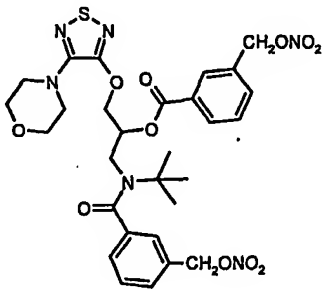


(3)

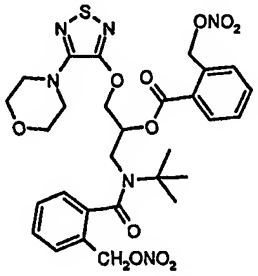
41. Compounds and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 20 and claim 24 wherein the compounds are:



(4)

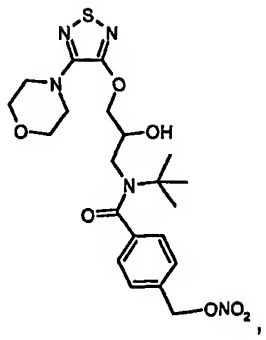


(5)

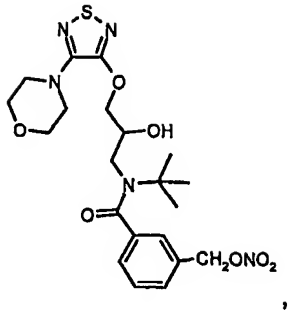


(6)

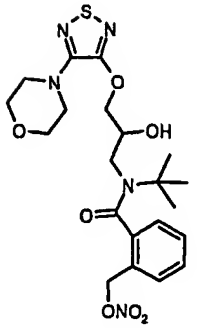
42. Compounds and the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof according to claim 30 and claim 34 wherein the compounds are:



(7)



(8)



(9)

43. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts according to claim 1 and claim 4 which is 4-(Nitrooxymethyl)benzoic acid (S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanoate maleate salt.

44. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts according to claim 1 and claim 24, which is 4-(Nitrooxymethyl)benzoic acid (S)-1-[(1,1-dimethylethyl)[(4-nitrooxymethyl)benzoyl] amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanoate.

45. A compound and the enantiomers, diastereoisomers and pharmaceutically acceptable salts according to claim 1 and claim 34 which is (S)-1-[(1,1-dimethylethyl)[(4-nitrooxymethyl)benzoyl]amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol.

46. A compound of formula (I) and/or the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof as defined in any of claims 1 to 45, for use as medicament.

47. Use of a compound of formula (I) and/or the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof as defined in any of claims 1 to 45 for preparing a drug that can be employed in the treatment or prophylaxis of hypertension, cardiovascular and vascular diseases.

48. Use of a compound of formula (I) and/or the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof as defined in any of claims 1 to 45 for

preparing a drug that can be employed in the treatment of glaucoma and of elevated intraocular pressure.

49. A pharmaceutical composition comprising a compound of formula (I) and/or the enantiomers, diastereoisomers and pharmaceutically acceptable salts thereof as defined in any of claims 1 to 45 and a pharmaceutical acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/013682

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D285/10 A61K31/433 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00/61541 A (NICOX S.A; DEL SOLDATO, PIERO) 19 October 2000 (2000-10-19) claims 1,5; example 4	1-49
Y	WO 01/12584 A (NICOX S.A; DEL SOLDATO, PIERO) 22 February 2001 (2001-02-22) claims 1,4; example 2	1-49
Y	US 4 801 596 A (SIMON ET AL) 31 January 1989 (1989-01-31) cited in the application column 2, line 38 - line 44; claim 1	1-49
Y	US 5 639 904 A (PRAT QUI+E,OTL N+EE ONES ET AL) 17 June 1997 (1997-06-17) cited in the application column 4, line 26 - line 31; claim 1	1-49

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 April 2005	11/04/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seelmann, I

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INTERNATIONAL SEARCH REPORT

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